Pelvic exenterations for advanced and recurrent endometrial cancer: clinical outcomes of 40 patients

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Abstract: OBJECTIVE The aim of this study was to analyze the clinical experience and outcome of patients who have undergone pelvic exenteration for primary advanced or recurrent endometrial cancer. METHODS We analyzed the medical records of 40 women who underwent pelvic exenteration to treat primary advanced or recurrent endometrial cancer. RESULTS Pelvic exenteration was performed in 40 patients with primary advanced or recurrent endometrial cancer. Three patients (8%) underwent a primary exenteration, and 37 patients (92%) underwent a secondary exenteration. A total exenteration, anterior exenteration, and posterior exenteration was performed in 85%, 5%, and 10% of patients, respectively.In 31 cases, exenteration was performed with a curative aim, and in 9 cases, exenteration was performed with a palliative aim. The overall survival rates were 61.4% at 5 years and 51.1% at 10 years. For the 31 patients who underwent pelvic exenteration with a curative aim, the overall survival rates were higher than those for the entire study population and were 72.6% at 5 years and 59.4% at 10 years. For the 9 patients who underwent a palliative exenteration, the overall survival rates were 19.1% at 5 years and 0% at 10 years. This is to the best of our knowledge the biggest study of pelvic exenteration in patients with endometrial cancer. CONCLUSIONS Our data show that pelvic exenterations are a valid therapeutic option with long-term survival in select patients.

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Pelvic exenterations for advanced and recurrent endometrial cancer: clinical outcomes of 40 patients

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Key words: pelvic exenteration, endometrial cancer, survival, radical surgery

Shortened version of the title:

Exenterations for endometrial cancer

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Synopsis

The study analyzed the clinical experience and outcome of patients who have undergone pelvic exenteration for primary advanced or recurrent endometrial cancer. The data show that pelvic exenterations are a valid therapeutic option with long-term survival in select patients.

Abstract

Background:

The aim of this study was to analyze the clinical experience and outcome of patients who have undergone pelvic exenteration for primary advanced or recurrent endometrial cancer.

Methods:

We analyzed the medical records of 40 women who underwent pelvic exenteration to treat primary advanced or recurrent endometrial cancer.

Results:

Pelvic exenteration was performed in 40 patients with primary advanced or recurrent endometrial cancer. Three patients (8%) underwent a primary exenteration, and 37 patients (92%) underwent a secondary exenteration. A total exenteration, anterior exenteration, and posterior exenteration was performed in 85%, 5% and 10% of patients, respectively.

In 31 cases, exenteration was performed with a curative aim, and in 9 cases, exenteration was performed with a palliative aim. The overall survival rates were 61.4% at five years and 51.1% at 10 years, and the disease-free survival rates were 70.5% at five years and 50.7% at 10 years. For the 31 patients who underwent pelvic exenteration with a curative aim, the overall survival rates were higher than those for the entire study population and were 72.6 % at five years and 59.4 % at 10 years. For the nine patients that underwent a palliative exenteration, the overall survival rates were 19.1 % at five years and 0 % at 10 years. This is to the best of our knowledge the biggest study of pelvic exenteration in patients with endometrial cancer

Conclusions:

Our data show that pelvic exenterations are a valid therapeutic option with long-term survival in select patients.

Introduction

Pelvic exenteration has been performed since December 1946 and describes a surgical procedure that involves the en bloc removal of reproductive organs, the bladder with the urethra, the pelvic ureter, the rectum and the sigmoid colon, including the anus and perineum. Alexander Brunschwig characterized the procedure in his article as, “the most radical surgical attack so far described for pelvic cancer”. The perioperative mortality rate at the time that article was published was 23%, and long-term survival rates were low [1].

Due to substantial improvements in operative and reconstructive techniques, the mortality and morbidity rates of pelvic exenteration have decreased and its survival rate is continuously increasing.

Currently, pelvic exenteration is absolutely considered as a treatment option for select patients with advanced gynecologic malignancies. These patients have often suffered a recurrence after either operation, irradiation or both.

The aim of this study was to analyze the outcome of patients who have undergone pelvic exenteration for primary advanced or recurrent endometrial cancer. These patients are normally older than patients with cervical cancer and, therefore, often have numerous comorbidities. Our data indicate that despite of these problems, pelvic exenteration for primary advanced or recurrent endometrial cancer is an option that is feasible with high survival rates and, therefore, should be considered as a treatment option for these patients.

Patients and methods

We retrospectively analyzed the medical records of 40 patients who underwent pelvic exenteration due to primary advanced or recurrent endometrial cancer. The study was approved by the local ethic committee.

Exenteration was indicated as the primary treatment when the uterine tumor had infiltrated the bladder and/or rectum inducing fistulas. The majority of cases were secondary exenterations performed after an initial operation with or without irradiation treatment; in those cases, the indication for exenteration was tumor recurrence that met the criteria for primary exenteration. All patients underwent a preoperative examination under general anesthesia to verify the presence of a tumor histologically and to evaluate the tumor's operability. This examination also included a cystoscopy and rectoscopy. Additionally, a computerized tomography (CT) scan was performed.

If the CT scan showed no evidence of metastasis, no intraabdominal metastases were found during the operation and clear margins were pathologically confirmed, the exenteration was considered curative. An exenteration was considered palliative in cases with distant metastasis, a positive peritoneal lavage or tumor perforation into the pouch of Douglas, and when positive margins were detected pathologically.

Among the 40 patients, 12 women (30%) had comorbidities, including four with hypertonia, two with diabetes or severe obesity, one with nicotine abuse and three with multiple comorbidities.

All exenterations were performed at the Department of Gynecology of the General Hospital Neumarkt and the Department of Gynecologic Oncology of the University Hospital Erlangen. In total, seven surgeons were involved in this study.

Anterior exenteration was defined as the removal of the uterus and vagina with the bladder, the pelvic ureters and the urethra, and posterior exenteration was defined as the removal of the reproductive tract with the recto-sigmoid colon. Total exenteration included the removal of both the anterior and posterior compartments.

Reconstruction included the formation of a continent ileocecal bladder (30/40) whenever possible; otherwise, conduits (4/40) and uretero-uretero-stomas (2/40) were constructed. In addition, 30 colonic neovaginas were generated using the caudal 10 cm of the colon above the resection. This portion of the colon was divided from the rest of the colon to preserve its blood supply and was then rotated 180°. Furthermore, the omental flap was used in 32 cases to provide much better pelvic filling, and this reduced the specific morbidity. Of the 40 patients, 31 (78 %) received complete continent reconstruction.

To restore bowel continuity, 37 colorectal or coloanal anastomoses were performed. In cases with high irradiation doses or extremely deep anastomosis, a temporary protective stoma was built for six weeks (16/40). Three patients required a permanent colostomy.

The survival analysis was performed using Kaplan-Meier curves and Greenwood 95% confidence bands. Survival curves were compared using the log-rank test. Fisher's exact test was used to examine the significance of the association between two variables in a 2 x 2 contingency table.

Results

Three patients (8%) underwent a primary exenteration, and 37 patients (92%) underwent a secondary exenteration. For the secondary exenteration cases, the disease-free period from initial treatment to the time of exenteration ranged from 4 to 111 months, with a median of 24 months.

Two (5%), four (10%) and 34 (85%) patients underwent an anterior, posterior and total exenteration, respectively. In 31 cases (78%), exenteration was performed with a curative aim, and in 9 cases (23%), exenteration was performed with a palliative aim.

The median patient age was 63.5 years with a range of 43 to 78 years. The mean follow up time after exenteration was 51 months, with a median of 35 months and a range of 1 to 263 months.

A lymphadenectomy was performed in 37 patients. Two, four, and 31 patients had undergone pelvic, paraaortic and both pelvic and paraaortic lymphadenectomies, respectively. Additional interventions, such as nephrectomy (3 cases), removal of small bowel sections (7 cases), removal of colon sections (3 cases) and vulvectomy (2 cases), were performed when necessary. Eight patients (20%) were found to have distant metastasis. Of the patients with a single metastasis, two had a metastasis in the abdominal wall and one each had a metastasis in the ovary, inguinal lymph nodes, mesentery and paravaginal tissue. Two patients showed multiple metastases intraoperatively.

The tumors were grade 1 in four cases (10%), grade 2 in 14 cases (35%) and grade 3 in 20 cases (50%). In two cases (5%), only post-irradiation scarring was found without evidence of a tumor. In 29 patients (73%), the tumor entity was an adenocarcinoma.

In 37 patients (92%), a pathological complete removal of the tumor was achieved, and three patients (8%) had positive margins. Two out of those 3 patients (66%), whom had undergone a primary exenteration, had clear margins. Clear margins were also found in 95% of patients (35/37) who underwent a secondary exenteration.

In 27 cases, no lymph node metastases were found. Two patients were positive for pelvic lymph node metastases and one patient was positive for paraaortic lymph node metastases. Additionally, seven patients were positive for both pelvic and paraaortic nodal metastases. Two of those patients (29%) had undergone a primary exenteration (Tab. 1).

The 30 patients with pathologically free lymph nodes had a 5-year survival rate of 63.3% and a 10 year survival rate of 57.0%.

The overall survival rate was 61.4% at 5 years and 51.1% at 10 years (Fig. 1). The disease-free survival was 70.5% at 5 years and 50.7% at 10 years. For the 31 patients who underwent pelvic exenteration with a curative aim, the overall survival rates were higher than those for the entire study population and were 72.6% at 5 years and 59.4% at 10 years (Fig. 2).

For the 9 patients that underwent a palliative exenteration, the survival rate was 19.1 % at five years and 0% at 10 years (Fig. 2). Two of those 9 patients died, one at 2 months after exenteration due to sepsis and one due to general weakness. Three patients died due to distant pulmonary metastasis, and one patient died due to a new tumor recurrence. Three patients, who were all at least 60 years old, were lost to follow-up after five, eight and 108 months.

The patients that were 43 to 55 years of age (8, 20%) had survival rates of 100% at 5 years and 75% at 10 years. The patients that were 56 to 64 years of age (14, 35%) had a survival rate of 61.6% at both 5 and 10 years. The patients older than 65 years (18, 45%) had survival rates of 40.2% at 5 years and 30.2% at 10 years. The difference in the overall survival rates between the youngest and the oldest cohort was statistically significant (p= 0.03). (Fig. 3).The eight patients that were between 43 and 55 years of age had a survival rate of 100% at 5 years. They all underwent an exenteration with a curative aim. The tumors were graded G0 (no tumor residual) for 1 patient (1/8, 12.5%), G1 for 1 patient (1/8, 12.5%), G2 for 2 patients (2/8, 25%) and G3 for 4 patients (4/8, 50%). No patient had metastasis in the pelvic lymph nodes. One patient had paraaortic lymph node metastasis, and 2 patients had metastases in the mesenteric lymph nodes.

Considering only the homogenous group of the 15 patients with adenocarcinoma who underwent exenteration with a curative aim and for whom pathological free margins were achieved, no lymph node metastases were present, and no evidence of lymphangiosis was observed, we achieved a survival rate of 77.5% at 5 years and of 64.6% at 10 years.

Complications occurred in 12 of the 40 patients (30%). Seven patients had one complication, such as abscess formation, ileus, fistula, lymph cyst, septicemia, thrombosis, etc. Two patients had two complications, and 3 patients had more than two complications.

In this study, which included many elderly patients, the cause of death was local recurrence for 2 patients and distant metastasis for 5 patients. For 12 patients, the cause of death was not tumor

related. At the time of this publication, 2 patients were still living, and their lung metastases had been removed. The perioperative mortality rate (30 postoperative days) was 7.5% (3/40).

Discussion

The main indication for pelvic exenteration is the central persistence or recurrence of gynecologic cancers. A major issue when comparing published data regarding pelvic exenterations is the heterogeneity of patient groups. In numerous papers, patients with different gynecologic cancers are not analyzed separately; therefore, the results of those papers should be interpreted with caution. The study presented here describes a series of a single gynecologic cancer entity, endometrial cancer, and solely depicts clinical outcome after pelvic exenteration. Although many parameters, such as perioperative morbidity and mortality rates after pelvic exenteration, are similar between different cancer types, there are some interesting distinctions that require closer consideration.

The first reported perioperative mortality rate for pelvic exenteration for primary advanced or recurrent endometrial carcinoma was 23% [1,2], and this has decreased to between 0 and 10% [3, 4, 5, 6]. In our study, there were no intraoperative deaths, and the perioperative mortality rate was 7.5%.

Morbidity rates of up to 75% have been reported by earlier publications [3,6,7,8,9]. Due to improvement in perioperative care, operative morbidity has noticeably declined over the last few decades. Our complication rate of 30% is within the reported range for pelvic exenteration, although 37 of our 40 patients (92%) were pretreated, and the majority of them were pretreated more than once (24/37, 65%). Regardless of these pretreatments, we achieved complete continent reconstruction of the neo-bladder and colon in 80% (32/40) of our patients. Of the initial 18 patients who underwent a protective colostomy, 8 were resected and 10 were maintained due to patient request.

The 5-year overall survival rate of the 40 patients with primary advanced or recurrent endometrial cancer was 61.4 %. The best outcome was observed in the youngest age group (43-55 years). All women in that group survived 5 years. For this age group, no advantage was found in regards to negative prognostic features, such as high grading (G3: 4/8, 50%). The oldest patient group (>65 years) had a 5-year survival rate of 40.2% and a 10-year survival rate of 30.2%, which indicates that pelvic exenteration is still a viable option for these patients, with a long-term survival rate. Furthermore, these data are in accordance with those of other authors [8, 9 10, 11, 12-17].

For patients undergoing pelvic exenteration with a curative intent, the survival rate of patients with primary advanced or recurrent cervical cancer is higher than that of patients with endometrial cancer: 72.6 % vs. 64% at 5 years and 59.4% vs. 57% at 10 years [25]. However, due to the small cohort in this study, this difference was not statistically significant (p= 0.70). This difference in survival rate may be due to the different biological behaviors (parametrial vs nodal invasion) of these two cancer entities and once again indicates the problem of analyzing outcomes after pelvic exenterations in an inhomogeneous cohort. Another observed difference between endometrial and cervical cancer is the presence of mesorectal lymph node metastasis without infiltration of the rectum. While mesocolic lymph node metastasis clearly decreases the 5-year overall survival of patients with cervical cancer [25], this was not found in patients with endometrial cancer . Of three patients with mesocolic lymph node metastasis, 2 patients experienced long-term survival with no other lymph node metastases, and one patient died after R1 resection shortly after the operation.

When major symptoms, such as pelvic pain, bowel obstruction and fistula formation, substantially reduce patient quality of live, palliative exenteration may be considered, not only to improve quality of live but also to improve survival. In support of this, the patients in our study who underwent palliative exenteration had a 5-year survival rate of 19.1%. Other therapy options, such as chemotherapy, radiation and the combination of the two, show overall survival

rates of a few months and sometimes cause severe side effects. In a phase II trial, patients with persistent or recurrent endometrial cancer receiving bevacizumab had a median progression free survival of 4.2 months and an overall survival of 10.5 months [26]. Several other phase II and III trials with single agent chemotherapy showed a limited response rate that typically lasted for only several months [27]. Due to the lack of alternative effective treatment options, pelvic exenteration may be a reasonable alternative.

Although patients with primary advanced endometrial cancer represent only a small portion of patients with newly diagnosed uterine cancers, they have a high percentage of disease-related deaths, with low survival rates in patients with advanced stage or recurrent disease [18, 19, 20, 21, 23, 26, 27]. Women with advanced stage or recurrent disease are often multimorbid, obese and older than women with other uterine cancers; thus, frequently, they are not considered ideal candidates for extensive surgeries, such as pelvic exenteration, even though studies have shown that mortality can be decreased when surgery is performed [22].

The limitations of our study are its retrospective character and relatively small cohort. However, the 40 cases presented here represent the largest patient cohort with advanced or locally recurrent endometrial cancer who underwent pelvic exenteration published to date. Only a few studies have compared pelvic exenteration to radiotherapy, and we did not find any studies that compared exenteration to chemotherapy. The limited data available demonstrate that pelvic exenteration may provide some benefit over radiation, although larger studies are necessary to support this finding [24].

Improvements in operative technique have resulted in the more frequent achievement of pathological free margins. There are limited treatment options available for women with advanced or recurrent endometrial cancer, and exenteration is the only treatment that provides the possibility of cure. Our finding of a five-year overall survival rate of 61.4 % supports the findings of other authors.

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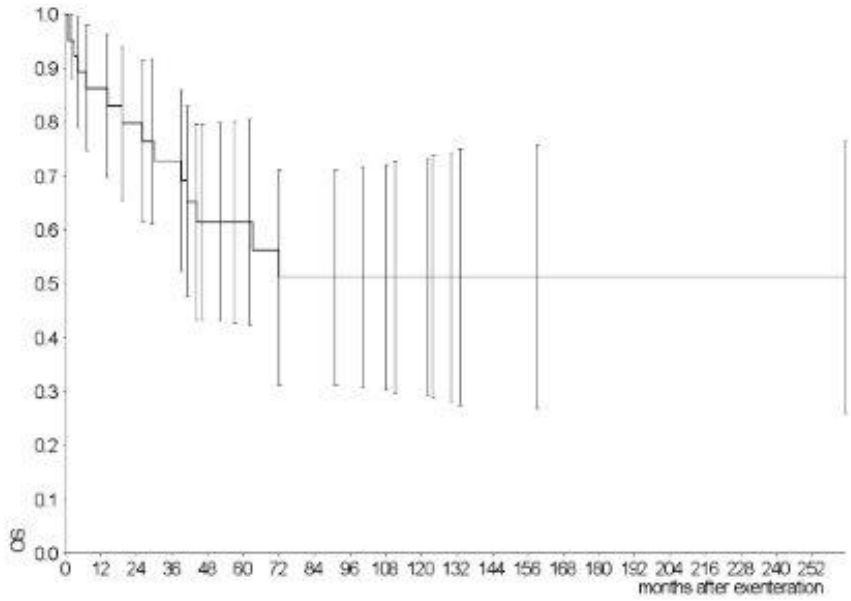
Figures:


1.0
0.9
0.8
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0.4
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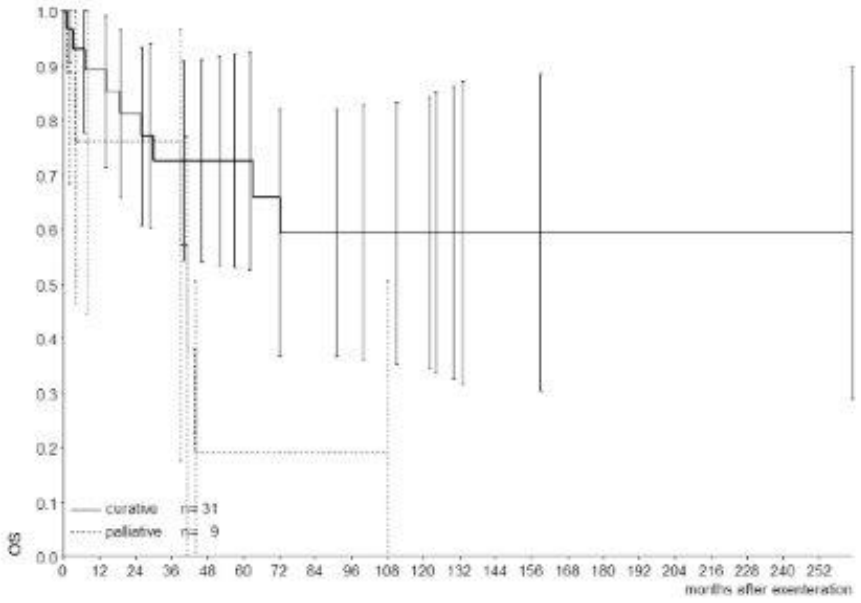
OS
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240 252
months after exenteration

Figure 1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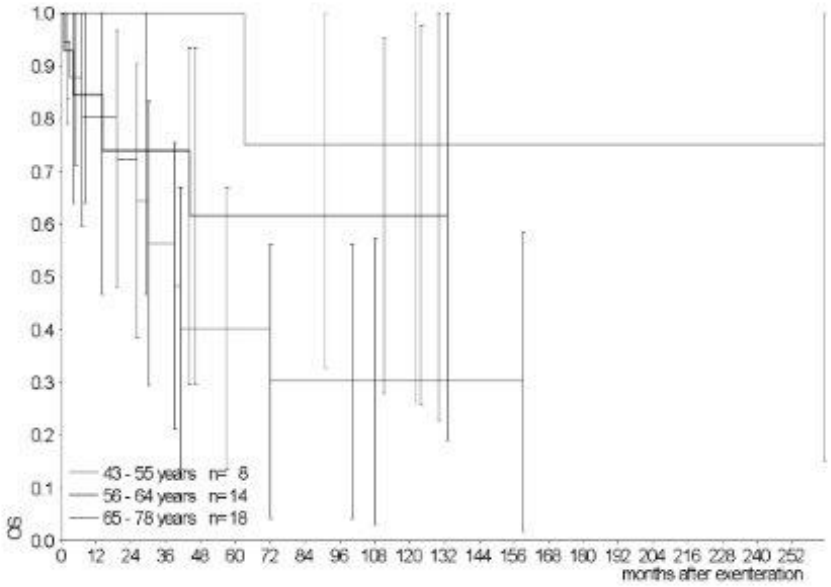
OS
curative n= 31
palliative n= 9
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240 252
months after exenteration

Figure 2


1.0
0.9
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0.5
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0.3
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0.1
0.0
OS
43 - 55 years n= 8
56 - 64 years n=14
65 - 78 years n=18
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240 252
months after exenteration

Figure 3

Pretreatment					Interval pretreatment/exenteration			Exenteration			
Form	Number	Lymph node status initial treatment		Chemotherapy	Min.	Max.	Median	Pelvic lymphadenectomy	Paraaortic lymphadenectomy	Pos. pelvic lymph nodes	Pos. paraaortic lymph nodes
None	3			0				3	2	2	2
Operation	12	Not performed	7	0	4	86	23	11	11	3	2
		Performed, missing report	1								
		Tumor-free	3								
		Metastasis	1								
Radiation	1			0	13	13	13	1	1	0	0
Operation and Radiation	24	Not performed	16	2	6	111	28	20	19	4	4
		Performed, missing report	0								
		Tumor-free	6								
		Metastasis	2								

Tab.:1